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## Epidemiology and clinical aspects of gout

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THE EPIDEMIOLOGY AND CLINICAL ASPECTS OF GOUT

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## INTRODUCTION

Gout has been recognized since antiquity as a clinical disease. It was originally called podagra from the Greek pous, foot and agra meaning attack. The term gout is derived from the Latin, gutta meaning drop.<sup>23</sup> Stedman's Medical Dictionary defines gout as "a disease of metabolism characterized by recurrent attacks of arthritis, particularly in the metatarsophalangeal joint of the great toe, though any joint may be attacked, by deposits of sodium biurate in and around the affected joints, and by inflammation of fibrous structures elsewhere."<sup>21</sup> The term gout may also be used to describe acute or chronic gouty arthritis or chronic deforming gouty arthritis.

Historically gout has been alluded to in many ancient writings. For example, we find in the Old Testament in 2 Chronicles, chapter 16, verse 12, "In the thirty-ninth year of his reign Asa was diseased in his feet, and his disease became severe; yet even in his disease he did not seek the Lord, but sought help from physicians."<sup>12</sup> It is certainly highly probable that the disease referred to in this passage of Scripture was gout, and this was written before the foundation of the Roman empire! Hippocrates, 460-370 B.C., knew gout as the unwalkable disease.<sup>11</sup> Likewise, many famous persons in history have had or are thought to have had gout. Among these are: Achilles, Oedipus, Henry VII, Martin Luther, Henry VIII, John Wesley, John Calvin, Francis Bacon, Oliver

Cromwell, Alexander the Great, Benjamin Franklin, Louis XIV, Goethe, Newton and Charles Darwin.<sup>23</sup> It has been estimated that approximately 800,000 persons in the United States alone suffer from gout so it is not a rare condition.<sup>9</sup> How many of those who suffer with gouty arthritis which is undiagnosed and untreated is anybody's guess. Since gout is one of the only types of arthritic condition which can be successfully treated it is indeed a pity that anyone should suffer from this disease.

#### EPIDEMIOLOGY

As mentioned above there are approximately 800,000 gout sufferers in the United States alone not to mention the untold thousands throughout the rest of the world.<sup>9</sup> The incidence of gout can only be estimated however, so there is a large divergence of opinion regarding the actual incidence. At any rate it is a fairly prevalent disease and one which causes almost intolerable pain in severe cases. Sidney Smith, an eighteenth-century clergyman, wrote, "When I have gout I feel as if I were walking on my eyeballs."<sup>5</sup>

Gout has by far its greatest incidence in the male. It is generally agreed that the sex incidence is 95.5% males and 4.5% females.<sup>5,9,23</sup> No good explanation has been given for this aberrant sex ratio but a number of possibilities have been suggested. It is thought that the ratio may be attributed to the hereditary transmission of gout. It has also been hypothesized that it may be due to a low fertility rate among married women with gout.<sup>23</sup> It has also

been suggested that women can tolerate a higher uric acid level without showing the overt clinical manifestations of gout. Whatever the cause the sex ratio of 95.5/4.5 has been well documented clinically.

The average age of onset of clinical manifestations of gout is about 45, but the first attack may occur as early as the first decade of life.<sup>5,23</sup> Other individuals may not have clinical gout until the 8th or 9th decade of life. It is highly probable that individuals who do not develop clinical gout until late in life have had a high serum uric acid for many years but for some reason have not developed the manifestations until late.

The race distribution of gout has not been well documented. Gout has been described in all parts of the world. It has been previously assumed that Negroes were more or less free of the disease, but as better methods of diagnosis are found and more interest is generated in gout it is being reported with greater frequency in Negroes.<sup>23</sup>

A seasonal incidence of acute attacks of gout has been described. It has been reported that attacks occur most commonly in early spring and late fall.<sup>29</sup> This seems to correspond with apparent changes in other types of arthritic and rheumatic conditions which occur during changes in barometric pressure and which allows the rheumatism sufferer to predict changes in the weather.

It has been formerly thought that gout was due to over indulgence in alcohol or food and that therefore it was a disease of

wealthy persons rather than the poor. However, we now know that gout is an hereditary disease and thus it attacks rich and poor alike.<sup>23</sup>

#### ETIOLOGY

Gout is one of a growing number of diseases resulting from a so-called "inborn error of metabolism".<sup>9</sup> That gout was associated with uric acid has been known for many years. Uric acid is a normally occurring product of metabolism. Persons with gout apparently produce an excess of this substance as evidenced by the fact that some gout patients have been shown to excrete excessive amounts of uric acid while on a low purine diet. Thus the uric acid concentration in the serum of gout patients is probably a result of overproduction rather than inability to excrete uric acid. However, a number of other possible causes for increased uric acid levels are believed to contribute to this condition. For example, decreased destruction of enzymes. It has been thought that a decreased destruction of the enzyme uricase was a possible factor in the occurrence of gout.<sup>7,17,23</sup> However, it is known that allantoin is the degradation product of uric acid in lower animals so uricase in man should result in this same end product. Nongouty humans, however, excrete only very small amounts of this substance daily so it hardly seems likely that a deficiency of uricase could result in full-blown gout.<sup>23</sup>

Another popular theory of the etiology of gout centers around

a diminished excretion of urates by the kidney. Here again is a theory that does not stand up under close scrutiny. If a high urate concentration in the serum is due to poor excretion by the kidney then other substances excreted by the kidney should also be improperly excreted. This is not found to be the case. Gout patients frequently exhibit no other abnormal functions. Also, studies evaluating the renal excretion of urates reveal little or no difference between gout patients and nongouty persons.<sup>23</sup> If renal impairment produced elevated uric acid levels and subsequent gout then we would expect patients with glomerular damage to exhibit elevated urate concentrations if not clinical gout. This, of course, has not been found to be the case.

The most satisfactory explanation for the metabolic deficiency producing gout is that there is an increase in uric acid formation resulting in an increase in the metabolic pool.<sup>23</sup> This explanation would be consistent with the increased excretion of urates frequently noted in gout patients.

#### URIC ACID METABOLISM

Uric acid is the end product of purine metabolism in man, but in the sub-primate mammals the uric acid is further oxidized to allantoin by the action of uricase. Thus in such animals the principal end product of purine metabolism is allantoin instead of uric acid.<sup>7</sup> In humans urea is the end-product of nitrogenous substances such as those of amino acid and pyrimidin origin. In



birds and reptiles uric acid is synthesized, and thus corresponds in its function to urea in man. Uric acid is apparently excreted in humans in almost constant amounts. Dietary intake, except for purine and nucleic acid substances, does not effect uric acid excretion to any great extent. The purine ring is made up of a number of constituents including glycine, which furnishes carbon atoms 4 and 5, carbon dioxide furnishing carbon atom 6, nitrogen atom 7, and atoms 2 and 8 are supplied by formate. The other nitrogen atoms come from glutamine and aspartic acid.<sup>23</sup>

The metabolism of uric acid in man has been studied most extensively by the use of isotopically labeled uric acid. This is accomplished by N<sup>15</sup> in carbon atoms 1 and 3. Single doses of the labeled uric acid were injected intravenously into a normal human subject and into patients suffering from gout.<sup>7</sup> The dilution of the injected labeled compound was used to calculate the quantity of uric acid which is present in the body water. This quantity is called the "miscible pool". In normal subjects the miscible pool contains an average of about 1130 mg. of uric acid. In subjects with gout, the miscible pool was much larger. In a mild case of gout with a serum uric acid of 6.9 mg./100 ml. and no symptoms the miscible pool contains about 4740 mg. of uric acid and ranges up to 31,000 mg. in patients with severe symptoms.<sup>7</sup>

It is possible to estimate the "turn-over" of uric acid from the rate at which the N<sup>15</sup> declines in the uric acid and this is the

rate at which uric acid is synthesized and lost from the body. It has been found that the uric acid formed in the normal subject is from 500-580 mg. per day. Due to the fact that the quantities of uric acid entering the miscible pool are greater than those lost by the urinary route it was found that some of the uric acid is not excreted but is broken down chemically. Some of this uric acid is excreted in the bile. Another portion, however, is degraded to other nitrogenous products.<sup>7</sup>

Uric acid is only slightly soluble and tends to precipitate in acid urine upon standing. This factor is probably responsible for the tendency to form renal calculi in the patient with gout.<sup>7</sup>

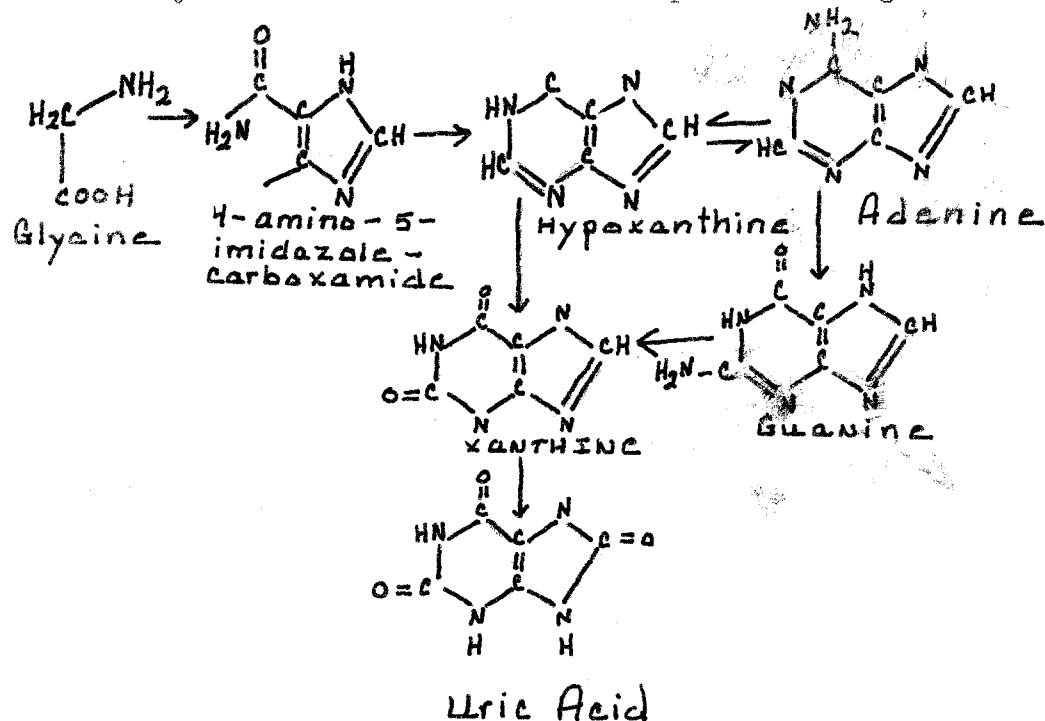


Fig. 1. Pathways of Purine Metabolism in the Human Body

## CLINICAL DESCRIPTION

The first sign of gout is usually an acute attack of arthritis in one or more of the joints of the extremities, and the diagnosis of gout is usually not suspected until after this first attack of arthritis. It is generally felt that a diagnosis should not be made until after this event. Other prodromal signs include such things as elevated blood pressure, albuminuria, and renal stones.<sup>23</sup> These latter findings may also remain manifest after the initial episode of articular distress.

The initial joint distress may appear at any time of the day or night and at any time of the year. The onset is sudden and usually involves the metatarsal-phalangeal joint of the great toe of either or both feet. The pain of any attack of gout including the first episode is often so severe as to be completely incapacitating.<sup>5,9,23</sup> It is generally held that the severe pain of gout is due to effusion into the joint cavity and by edema of the surrounding tissues. Several joints may be involved simultaneously during an acute attack, or several joints may be involved successively as in migratory polyarthrititis of rheumatic fever. A gout infected joint may also be confused with a septic process in that the cardinal signs of inflammation are present.<sup>23</sup> This inflammation often extends beyond the affected joint to involve the lymphatics as in a cellulitis. It is apparent that one must differentiate between a septic joint and a gouty joint so that incision and drainage will

not be attempted on a gouty joint or neglected on a septic one. In a gouty joint the skin is tense and shiny, and the color is better described as a cyanotic purple than a fiery red.<sup>5,23</sup> This is not always the case, however, and it should be pointed out that acute gouty joint involvement may occasionally be indistinguishable clinically from joint sepsis. The systemic reaction to acute gout may be even more difficult to distinguish from sepsis. The acute attack of gout may be accompanied by fever, chills, anorexia, headache, and a general feeling of malaise. Other points in the clinical picture to look for include the exquisite tenderness of the involved joint, engorgement of the veins in the region, and edema which may extend well beyond the limits of the involved joint. Another characteristic sign of gouty arthritis occurs after about a week and is found in none of the other arthritides. This is the desquamation of the skin over the affected joint, and may resemble cellulitis in its appearance.<sup>23</sup>

The diagnosis of gout although fairly easy to make is frequently missed because the clinician fails to consider gout when a patient has an acutely inflamed joint. Also, many clinicians look upon gout as primarily a European disease occurring predominantly in persons who drink excessive amounts of beer.<sup>5</sup> Excessive indulgence in either food or drink as a cause of gout has not been born out clinically although such overindulgence has been implicated in precipitating an acute attack in persons who suffer from gout.<sup>5,19,20</sup>

A number of other substances or factors are likewise suspected in precipitating acute attacks. These include drugs, sex, trauma, blood loss, acute infections, prolonged bed rest, and surgical procedures.<sup>23</sup>

Drugs which have been implicated as inciting agents include vitamin B<sub>12</sub>, insulin, diuretics, thiamine chloride, ergotamine tartrate, and penicillin.<sup>23</sup> The fact that penicillin has been shown to precipitate attacks of gout and to aggravate the condition when it exists is another good reason for making a reasonable effort to differentiate between gout and sepsis in a case of an acutely inflamed joint. However, the fact that a specific drug has been implicated as an inciting agent in gout should never prevent a physician from using that drug when indicated by other pre-existing or concomitant conditions. Such drugs should not be used without careful consideration however.

Direct trauma as a precipitating agent in gout may be readily explained by the fact that there is frequently urate deposition in persons subject to gout and a blow to such an area could more easily produce acute inflammation. Persons with gout should be especially careful to have properly fitted shoes because ill-fitting shoes could easily provide sufficient trauma to precipitate an attack of gout.

The most important feature in the early diagnosis of gout and gouty arthritis is the history.<sup>5</sup> First of all a family history of gout should immediately alert the attending physician to the

possibility of gout as the diagnosis. Likewise, the history of the onset of the acute attack should lead to the correct diagnosis. Characteristic of an acute attack of gout is the speed of onset. A typical story may be that the patient goes to bed feeling perfectly well and awakens a few hours later with excruciating pain and swelling usually in the great toe of either foot.<sup>5</sup> The severity of the pain is another differentiating point in making the diagnosis of gout. The pain may be so severe that even the weight of bedding is intolerable. The duration of the first attack also aids in making the diagnosis of gout. The usual duration of the first attack is from five days to about ten days or two weeks.<sup>5</sup> The symptoms usually disappear rather suddenly leaving the patient with no residual complaints. Another notable characteristic of gout is the periodicity of the attacks which usually occur every six months to year and a half. The attacks gradually become more frequent and a more chronic phase is reached, usually after about two decades, in which the pain and discomfort may be almost constant. This is usually known as the chronic tophaceous phase. Between the acute attacks in patients without joint deformities there are no overt signs or symptoms. These periods of quiescence in the course of gout are known as the intercritical periods.<sup>23</sup>

The tophi, which are used by all too many clinicians as diagnostic criteria, but which usually do not appear until well after the diagnosis should have been made, are the result of urate

deposition in subcutaneous tissues. These urates are the salts of uric acid and are not usually deposited as subcutaneous tophi until the gout has been present for some time; however, tophi may rarely be present by the time of the first attack. The classical site of tophi is on the ear, and these may be identified as white nodules on the helix in long standing cases of gout. Other common sites for tophi include subcutaneous tissues over joints of the hands and feet, the olecranon bursa, the knees, and, less commonly, the buttocks.<sup>23</sup>

Another important diagnostic feature in gout is the elevation in the serum uric acid concentration. This elevation is invariably found in gout patients, but an increased concentration of uric acid does not always produce clinical gout. Gouty patients have elevated uric acid levels before and during acute attacks as well as during the intercritical periods unless uricosuric agents are administered. The normal level for uric acid in the serum is 2 to 5 mg./100 ml. Gouty patients usually have serum uric acid levels of 6 mg./100 ml. or greater. Uric acid levels of 10 to 12 mg./100 ml. are not infrequent in gouty patients.<sup>7,23</sup>

Other criteria which may aid in making the initial diagnosis of gout include urate stones or calculi, albuminuria, hypertension, and increased sedimentation rates.<sup>23</sup> As a matter of fact, urate lithiasis and hypertension may precede the initial attack.

In addition to laboratory diagnostic aids we would most certainly

wish to make use of radiographic evidence. However, it must be noted that gouty patients do not always exhibit abnormalities detectable by X-ray so roentgenographic studies may be counted on only for aid in the diagnosis of gout, and only in some of the patients. In any case, however, radiographic studies should be employed in any patient suspected of having gout.

The metatarsal-phalangeal joint of the great toe is often one of the first areas to show changes on X-ray. There is usually a narrowing of the joint space with bony overgrowth at the joint margins. There may also be some decrease in density of the head of the first metatarsal adjacent to the joint space. Soft tissue swelling is also usually in evidence even in the absence of other demonstrable bony changes during the acute phase of the disease. Tophi are exhibited on X-ray as circular or ovoid areas of decreased density with distinct and sharply defined margins.<sup>23</sup>

One other factor which may be of diagnostic value is the response of the patient to colchicine therapy. It is generally held that if colchicine is used for diagnosis full therapeutic amounts should be given. Likewise, since colchicine therapy may interfere with results of laboratory tests for gout, any patient taking colchicine or any other uricosuric drug should have those drugs withheld for 48 hours or more before any other diagnostic laboratory tests are obtained. A favorable response to a uricosuric drug by a patient suspected of having gout on the basis of other factors



makes the diagnosis of gout virtually certain.

#### DIFFERENTIAL DIAGNOSIS

Since there are a number of conditions which simulate gout and gouty arthritis it is necessary to be able to recognize these conditions and rule them out when attempting to diagnose a case of gout. Acute rheumatic fever and acute gouty arthritis are very difficult to differentiate. The age of the patient may be of some help in differentiating but certainly cannot be used as the sole factor since older persons may have rheumatic fever just as young individuals may have gouty arthritis. Articular distress is usually more acute in gout than in rheumatic fever. The sex incidence may also be of significance. A young female patient with acute arthritis is much more likely to have rheumatic fever than gout. Likewise, an elderly male with articular complaints is more likely to have gout. Electrocardiographic changes and cardiac symptoms favor a diagnosis of rheumatism. Other differentiating factors include response to colchicine and radiographic evidence. X-rays of rheumatic joints show soft tissue swelling only without evidence of bony changes.

Another significant disease which must be ruled out before making a diagnosis of gouty arthritis is rheumatoid arthritis. The differential in this case should not be so difficult to make. In rheumatoid arthritis the joints tend to be involved symmetrically, and the onset is not so sudden nor the articular pain so unbearable.

The duration of attacks is longer for rheumatoid arthritis than for gout. This is not to say that these two conditions cannot occur concomitantly in the same patient, in which case the differentiation would be fore difficult but less necessary. Of course, the final diagnosis may always be readily made histologically from biopsy of a tophus or a synovial membrane.

In older patients osteoarthritis, or degenerative joint disease, must be considered in the differential diagnosis with gouty arthritis.<sup>13</sup> The Heberden's nodes, which occur on the terminal interphalangeal joints, may somewhat resemble the tophi found in gout. It seems, however, that women are more prone to the development of acute Heberden's nodes; therefore, since women seldom have gout, the differentiation here should usually be relatively easy. Also, acute articular symptoms are rare in osteoarthritis and are the rule in gouty arthritis.

Septic joint involvement has been mentioned previously in the section on diagnosis. However, it should be mentioned again since the symptoms of sepsis in a joint will probably most closely resemble those of gouty arthritis. A septic joint, like a gouty joint, may be red, warm to the touch, swollen, and extremely tender, although probably not quite so exquisitely tender as a gouty joint. It should be again emphasized that it behooves the attending physician to attempt to differentiate these two conditions because of the fact that antibiotics may aggravate gout.

## PREVENTION AND TREATMENT

Since gout is generally held by authorities to be a disease of hereditary origin there is little in the way of prevention that can be done unless one is able to pick his ancestors. This, we must presume, lies beyond the scope of medical science, at least for the present. It is known that persons, especially males, whose parents or grandparents have gout are much more likely than others to have elevated serum uric acid levels, if not clinical gout. Most authorities would probably agree that relatives of known gout patients who have hyperuricemia without symptoms should be informed that they are potential gout victims. Such individuals should avoid obesity, excessive trauma to joints, and high purine foods. Hyperuricemic individuals should be identified by the physician as potential gouty patients so that when and if the initial acute attack occurs it may be correctly diagnosed and the proper treatment recommended. Of course therapy in gouty subjects should be directed toward the prevention of the chronic tophaceous manifestations which may be disabling in severe cases. This can be done with proper therapy in a cooperative patient.

It has been previously stated that gout is the only arthritic condition that can be effectively treated at present. Therefore, it is proper that considerable attention be paid to the treatment of gout. It should be understood at the beginning that gout cannot be cured. It is, however, a chronic disease that can be effectively

treated to reduce the number of acute attacks and to prevent the chronic manifestations. It is this "treatment" with which we will concern ourselves here.

Colchicine is one of the oldest drugs in the pharmacopeia and has been known for many years to be specific in the treatment of gout.<sup>23</sup> The autumn crocus or *Colchicum autumnale*, the source of colchicine, has been in use since 600 A.D. according to Graham.<sup>5</sup> However, the mechanism of the action of colchicine remains a mystery even today. This drug is the active principle of the tincture of colchicum and is present in many species of plants of that genus. It is not an analgesic drug and is useless as treatment in other types of arthritis. Another important fact is that colchicine is not a uricosuric agent, nor is it a diuretic. Colchicine seems to be specifically effective for regular use as a prophylactic agent in the gout patient, and it is especially helpful in relieving the symptoms of the acute attack of articular distress. In treating the acute attack it is recommended that colchicine be given in doses of 1 mg. every two hours for five doses the first day of the attack and in smaller doses as the attack diminishes. If very rapid action is necessary or desired colchicine may be administered intravenously in doses of 2 to 3 mg. given slowly.<sup>5,20,23</sup> This produces dramatic relief in about three hours. Because of its irritating effect, care should be taken to place the colchicine directly into the vein and not into tissue.

As mentioned above colchicine is recommended for use during the intercritical period between acute attacks. In this capacity dosages of 0.5 mg. are given three or four days each week in the milder cases, and one tablet each day in more severe cases.<sup>20</sup> The use of colchicine has been found to be beneficial in prophylaxis against the acute attack especially in combination with Benemid which will be discussed later. Colchicine is apparently well tolerated when taken over long periods of time and sensitivity does not seem to develop.<sup>23</sup> Unfortunately the toxic and full therapeutic doses are very close together, and this fact is frequently used to determine the maximum tolerable dose for a given patient with severe gout.<sup>20</sup> The toxic or side effects of excess colchicine intake are usually confined to the gastrointestinal tract. These symptoms include nausea, vomiting, and abdominal pain. Gastrointestinal upset is apparently not a factor when the drug is administered intravenously, so this route is recommended for attacks of gout which have been precipitated by surgical trauma.

Phenylbutazone (Butazolidin) is another drug which is effective in the treatment of gout when administered orally.<sup>23</sup> This drug has the advantage of being an excellent analgesic agent as well as having anti-inflammatory properties. Phenylbutazone should be started soon after the onset of symptoms. A large initial dose of 400 to 600 mg. is followed two hours later by 200 mg. and four hours after that by another 200 mg., thus making a total of 800 to

1000 mg. for the first day. The following two or three days 400 mg. daily should be given in divided doses until symptoms have disappeared. The relief of symptoms with this drug is rapid, but numerous undesirable side effects may result. Among these are salt and water retention which may lead to congestive heart failure and acute pulmonary edema. Nausea, vomiting, nervousness, insomnia, skin rashes, blurring of vision and bone marrow depression have also been attributed to phenylbutazone.<sup>23</sup> Thus phenylbutazone is not recommended for long term or prophylactic administration.

Probenecid (Benemid) (p-(di-n-propylsulfamyl)-benzoic acid) was synthesized following the observation by Wolfson and associates in 1948 that carinamide inhibited uric acid reabsorption.<sup>23</sup> Benemid has no analgesic or anti-inflammatory properties and is of no value in controlling the acute attack of gout. Neither is it a cure for gout. As a matter of fact, Benemid has been found to actually increase the number of acute attacks during the first few months of its administration. However, this drug has been found to be of significant value in the prophylaxis of acute attacks when it is used conscientiously over periods of several months to several years. Benemid seems to be more effective when used in combination with colchicine.

Benemid, unlike colchicine, is a urate diuretic drug or, as it is more commonly called, a uricosuric agent. It acts by reducing the tubular absorption of glomerular filtered urate and is

associated with an increased excretion of uric acid in the urine, a decreased concentration of uric acid in the serum, and a decrease in the metabolic pool.<sup>4,23</sup>

Probenecid was originally developed for the specific purpose of inhibiting renal tubular secretion of penicillin. This property was extremely useful in the early days of penicillin when this substance was scarce and expensive.<sup>14</sup> Since penicillin is excreted as penicillin and is not broken down or detoxified in the body it is obvious that an agent which would prevent tubular secretion of this drug would be very useful in maintaining adequate blood levels of the antibiotic. It was later found that probenecid was useful as a uricosuric agent and it is in that capacity that this drug is used to a great extent. Sirota and associates reported in 1952 that Benemid has no significant effect on glomerular filtration, and that "data obtained support the complete filtration-partial tubular reabsorption concept of urate excretion in the normal and gouty subject and indicate that Benemid uricosuria is the result of a highly selective inhibition of tubular reabsorption of filtered urate".<sup>18</sup>

Apparently there is some antagonism between Benemid and salicylates, which are uricosuric in their own right. For this reason it is recommended that these two agents not be used simultaneously.<sup>4</sup> There do not seem to be any significant toxic side effects of Benemid. Also, mild renal dysfunction is not a

contraindication to the use of Benemid.<sup>23</sup> Patients who have been on Benemid therapy for prolonged periods may even show improved renal function as evidenced by blood urea nitrogen determinations. This is thought to be due to the fact that Benemid may cause gradual depletion of urate deposits which, when present in the kidney, may interfere with renal function to some degree.

In addition to the drugs discussed above, adrenal steroids have been used in treatment of gout. These agents, while they may be helpful in treating acute symptoms, are not recommended for prolonged administration. Likewise, the salicylates, acetylsalicylic acid and sodium salicylate, have long been known to be useful in treatment of gout. Their chief merit probably lies in their analgesic properties. As previously mentioned, however, there is some sort of antagonism between salicylates and probenecid which makes it inadvisable to use these two agents together.

In general there are about four stages of gouty disease each of which is somewhat unique in its therapy. These stages are as follows: stage I, the stage of asymptomatic hyperuricemia; stage II, the acute attack; stage III, the intercritical periods; and stage IV, the stage of chronic gouty arthritis.

Hyperuricemia, as has been previously mentioned, is frequently found in relatives of gout patients. In general, this condition should serve only to alert the physician to the possibility of gout in such persons so that the proper diagnosis can be made in the case



of acute onset of articular distress. There is no actual therapy during this stage because only a percentage of such persons will actually demonstrate clinical gout during their lives. However, the physician can recommend the avoidance of obesity, joint trauma, and high purine diets for these people.<sup>20</sup> Likewise, periodic checks should probably be made of the uric acid level to keep track of any progression of the disease.

The actual diagnosis of gout is not usually made until the appearance of the first acute episode of joint distress. The diagnosis should then be positively made. As mentioned above, a history of hyperuricemia makes the diagnosis much easier because the attending physician will be immediately alerted to the diagnosis. At any rate this is stage II, the acute attack, and it is here that the treatment of gout first begins. Colchicine should be administered at the first sign of articular distress in order to ward off the severe pain so characteristic of acute gout. Colchicine tablets, available in 0.5 mg. (1/120 grain), should be taken every hour or two until pain is relieved or the toxic symptoms occur. Control of the usual attack will require from eight to sixteen tablets.

Known gout sufferers should never be far from a supply of colchicine tablets because the earlier the medication is started during an acute attack the quicker relief will be attained.<sup>23</sup> It has been previously stated that probenecid may precipitate acute attacks during the first few months of its administration. It should be pointed out

here that if an acute episode of gouty arthritis occurs during probenecid therapy, colchicine or phenylbutazone is indicated in therapeutic amounts, but the probenecid should be continued without change in dosage.

Stage III, the intercritical periods, which will comprise the greatest length of time in the early years of a gout patient's history, should probably receive special attention. The aim of therapy during the intercritical periods is to reduce or prevent recurrences of acute articular distress. The best therapy is the combination of colchicine with Benemid. Colchicine will relieve the acute attack and may be given over long periods of time without the appearance of toxicity or increased tolerance. It has been found that patients who have been on colchicine for many years will still receive a full therapeutic response to this drug during an acute episode. Benemid, on the other hand, is effective in lowering the uric acid level of the serum and thus will frequently prevent the occurrence of acute episodes by bringing the uric acid down to normal levels. As much as 2 Gm. of Benemid per day may be given to severely afflicted persons. It is recommended that a high intake of fluids be maintained during a high dosage regimen in order to inhibit precipitation of urates in the renal tubules.<sup>22</sup> Since Benemid causes an increased excretion of urates, it makes sense to offer the kidney a large volume of water with which to carry away this increased volume of urates. An alkaline urine is also considered

to be helpful in the prevention of urate deposition in the kidney.<sup>4</sup> This can be accomplished by administration of sodium bicarbonate. Alkalinization should be continued as long as uricosuric therapy is causing an excess production of uric acid in the urine. The excess tends to decline as the miscible pool approaches normal.

Probenecid is excreted only by glomerular filtration and disappears slowly from the circulation even in the presence of impaired renal function. A daily dose of probenecid of 2 Gm. is sufficient to sustain, in normal persons, a plasma concentration between 4 and 10 mg./100 ml. It is possible to chemically evaluate the plasma concentration of Benemid, but the PSP test is a sensitive indicator of inhibition of renal tubular function by Benemid. If the PSP is depressed during Benemid therapy, this indicates that the uricosuric and penicillin enhancing effects will also be present.<sup>4</sup>

Stage IV, the stage of chronic gouty arthritis, represents the end result of long term gouty disease. This stage is characterized by the presence of tophi and low grade aches of the involved joints. It is hoped that, if proper management of the disease is exercised by the physician, there will not be a progression to this advanced stage. However, should this stage be reached in the natural history of gout it is well to be prepared to treat it.

The drugs used for treatment of stage IV are the same as those recommended for stage III, e.i. colchicine and Benemid. Since acute

attacks of joint distress may still occur during the chronic tophaceous stage it is necessary to maintain the patient on colchicine. It should be noted here that the response to treatment of the acute episode may not be as rapid or complete as during earlier stages, and several courses of colchicine may be necessary to bring such an attack under control.<sup>19</sup> It is in the treatment of this chronic stage that Benemid becomes almost indispensable. By causing an increased excretion of urates this drug produces a reversal of the flow of urates from subcutaneous and articular areas and thus effects a decrease in the size of existing tophi and prevents the formation of any new tophi. The dosage is the amount needed to reduce the serum uric acid level to normal. If renal calculi are present the dosage should be no greater than 0.5 to 1.0 Gm. per day. Of course a large fluid intake as well as alkalization of the urine should be employed as discussed above.

By following the therapy outlined above for the various stages of gout it is possible to keep most gout patients symptom-free while not restricting the patient severely in diet or activity. It is generally agreed that temperance should be exercised by the patient as far as alcoholic and high purine food intake is concerned but total abstinence is not necessary.

#### PROGNOSIS

A paper dealing with a disease such as gout would not be complete without a discussion of the prognosis. As was stated above,

none of the arthritic conditions is curable. Gout, however, is the one such condition which can be effectively treated and controlled. We should repeat here that in order to effectively treat a gouty patient it is extremely important that the patient cooperate. Patients who fail to follow the physician's orders or fail to take their medications regularly will, in all probability, continue to suffer from the malady. However, the prognosis in cooperative patients is good in general. This is especially true if the disease is diagnosed and treatment instituted early.

One of the most ominous prognostic signs is the formation of renal calculi and severe renal disease. It has been previously pointed out that renal calculi may be treated effectively by Benemid therapy, and that renal function may be improved by the chemical removal of such calculi. However, if primary renal disease or renal vascular disease is present the prognosis is much poorer because the effectiveness of the drugs depends upon the kidneys. In general, however, gout is the most gratifying of the arthritides to treat, and the prognosis is to be considered quite good from the standpoint of control of symptoms and chronic manifestations of the disease.

#### SUMMARY

On the preceding pages we have endeavored to present a concise but complete picture of gout. Gout is a disease which has plagued man for centuries, being mentioned in early writings including the

Bible. Unlike other arthritic conditions, gout is treatable. It is now generally accepted that anyone who suffers from gout does so needlessly. Herein lies the responsibility of the physician, e.i., to make an honest effort to rule out a diagnosis of gout before allowing a patient to suffer with this condition thinking it is a nontreatable form of arthritis.

Gout is known to be an hereditary disease, and its incidence is obviously sex-linked since it attacks males in a ratio of 95.5/4.5 over females. It is also included among the "inborn errors of metabolism" and is linked to purine metabolism and uric acid concentrations in the serum. Recent studies using isotopically labeled uric acid have confirmed and clarified much of the etiology of gout.

The clinical aspects of gout with its severe joint distress are included in detail in the preceding pages. Gout should be considered in the differential diagnosis of any acute inflammatory joint.

The currently accepted combined therapy using both colchicine and probenecid is described in some detail, as well as the pharmacologic background and action of these drugs. Although other drugs may be useful in treatment of gout it is felt that the above drugs provide the best advantage for continued long-term therapy.

#### ADDENDUM

Since the completion of this manuscript, certain articles have come to my attention which appear to shed new light upon the possible mechanism of action of colchicine in the treatment of gout.

Seegmiller and Howell, in an article published in June of 1962, proposed that colchicine diminished the metabolic activity of the leukocyte which causes decreased phagocytosis and lactic acid production. They hypothesized that this would interrupt the cycle of rapid crystal deposit, inflammatory response and phagocytosis of those crystals which is characteristic of acute gout. These two investigators were able to demonstrate an in vivo as well as an in vitro effect of colchicine at therapeutic levels. They pre-treated gouty volunteers with therapeutic doses of colchicine and found that the inflammatory response to the injection of sodium urate crystals was substantially reduced. They demonstrated the decreased phagocytosis effect of colchicine in an in vitro system using urate crystals and human leukocytes. Since phagocytosis increases lactic acid production by granulocytes, they reasoned that a decrease in phagocytosis might sufficiently reduce the local lactic acid production to interrupt the cycle mentioned above.<sup>31,32</sup>

Snodell published a student thesis in August of 1962 which suggests that colchicine may have some effect upon the metabolism of purines. He found that the rat intestine is able to convert

various purine compounds to uric acid under in vitro conditions. He observed that colchicine stimulated the oxidation of hypoxanthine to uric acid by the rat intestine. Colchicine appeared to inhibit the conversion of inosine, the riboside of hypoxanthine, to uric acid. He offered no explanation of these findings but suggested that "colchicine may exhibit its therapeutic properties in gout by altering some phase(s) of purine metabolism".<sup>33</sup>

Thus we see that there is evidence to support at least two possible mechanisms of action of colchicine in gout. While either of these possibilities seems plausible as an explanation of the action of colchicine, the fact that there are two such possibilities only serves to emphasize the fact that in all probability the final word on the mechanism of action of colchicine in gout has not been written. This topic certainly remains open for further investigation. While many of the actions of colchicine are known, its action in gout remains today mostly within the realm of hypothesis.



## CONCLUSIONS

Acute joint distress may be the primary manifestation of a number of diseases which we usually place in the general category of arthritic conditions. Undoubtedly some of the so-called arthritis sufferers are actually enduring needless pain and discomfort of treatable gouty arthritis rather than one of the untreatable forms. This is needless suffering because with proper diagnosis and careful management almost untold relief could be afforded these people. It is the responsibility of the physician to recognize these persons and possibly prevent their suffering from gouty arthritis. I believe that the greatest fault of physicians is their failure to think of gout as a possibility in cases of acute joint distress. Yet the diagnosis of gout, once it is thought of, is not difficult. Any male patient with articular distress who is in the middle age group should be considered a prime candidate for gout, especially in the presence of a family history of gout.

The serum uric acid level may virtually cinch the diagnosis of gout; however, this test is not particularly easy to perform and a reliable laboratory should be consulted for this determination. It should be remembered that uric acid level may not accurately reflect the severity of the clinical manifestations. Some persons may show symptoms of gout at relatively low uric acid concentrations while others may be symptom free at much higher uric acid levels. In general, however, no attempt to diagnose the condition should be

made until after the occurrence of the first acute attack of joint distress. Since gout is hereditary and thus a familial disease, all close male relatives of gout sufferers should have uric acid determinations to discover nonsymptomatic hyperuricemias. Any such relative who is found to have a hyperuricemia in the absence of symptoms should be informed of this fact and its implications. He should also be noted by the physician as a potential gout patient so that when articular symptoms do develop the correct diagnosis may be made and treatment instituted early.

Many of the ideas previously held by physicians concerning gout have been dispelled by closer evaluation and recent studies. For example, it has long been thought that gout was a disease acquired mainly by Europeans from overindulgence in food or drink. We now know that gout is an hereditary condition, and is very little, if any, affected by diet. Since uric acid is a product of purine metabolism, it is advisable for severe gout sufferers to abstain only from those foods which are high in purines.

The essential thing to remember is that the diagnosis of this disease is the responsibility of every physician who practices general medicine and treats arthritic conditions. Since gout is the only one of these painful conditions which can be effectively treated and relieved the physician should make special effort to determine whether any of his arthritic cases could possibly have been originally misdiagnosed, and whether one of his "arthritis"

patients may, in fact, be suffering from the treatable condition of gout. I believe that physicians should periodically review their cases of arthritis patients to seek out possible gout sufferers, and to attempt relief of their suffering. Serum uric acid determinations should be a principal part of the work-up of every case involving articular distress. Likewise, as has been previously mentioned, relatives of gout patients should be carefully screened as possible future gout patients. This is especially true of males. The most important aspect in the diagnosis of gout remains, however, merely to think of it as a possibility.

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